



The Power of Biorepositories for Research

The Tissue Issue: Ethical and Legal Issues in Biorepository Research

National Cancer Institute

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My Thoughts Today

- 2007 Status of cancer, NCI and cancer research: Why are Biospecimens critical? Were they always?
- Are there examples of the impact of biospecimens on research?
- What is NCI's view of Biospecimen/Biorepository issues and problems?
- What has/is NCI Doing to Address the Issues?
- Are there programs where the quality of biospecimens are critical?
- What do we see as legal, ethical and policy barriers?
- What does the road ahead look like?

NCI's Vision for Cancer and the Nation's Healthcare System

An interoperable "system" of evidence based molecular oncology where disease is either prevented or detected early and treated on an evidence-based and personalized basis

21st Century Personalized Medicine (Molecular Oncology) (Quality Biospecimens are Key to Progress)

20th Century (Not Sustainable)

- Focus on treatment
- Diagnosis based on morphologic and pathologic analysis
- Expensive; perpetuates unsuccessful approaches
- No systematic connection between research and clinical care

21st Century

- Focus on predisposition, early detection and biological processes
- Diagnosis based on molecular characterization and biological processes
- Evidence-based; continually assesses standard of care
- Connects bench → bedside → bench in seamless *feedback loop*

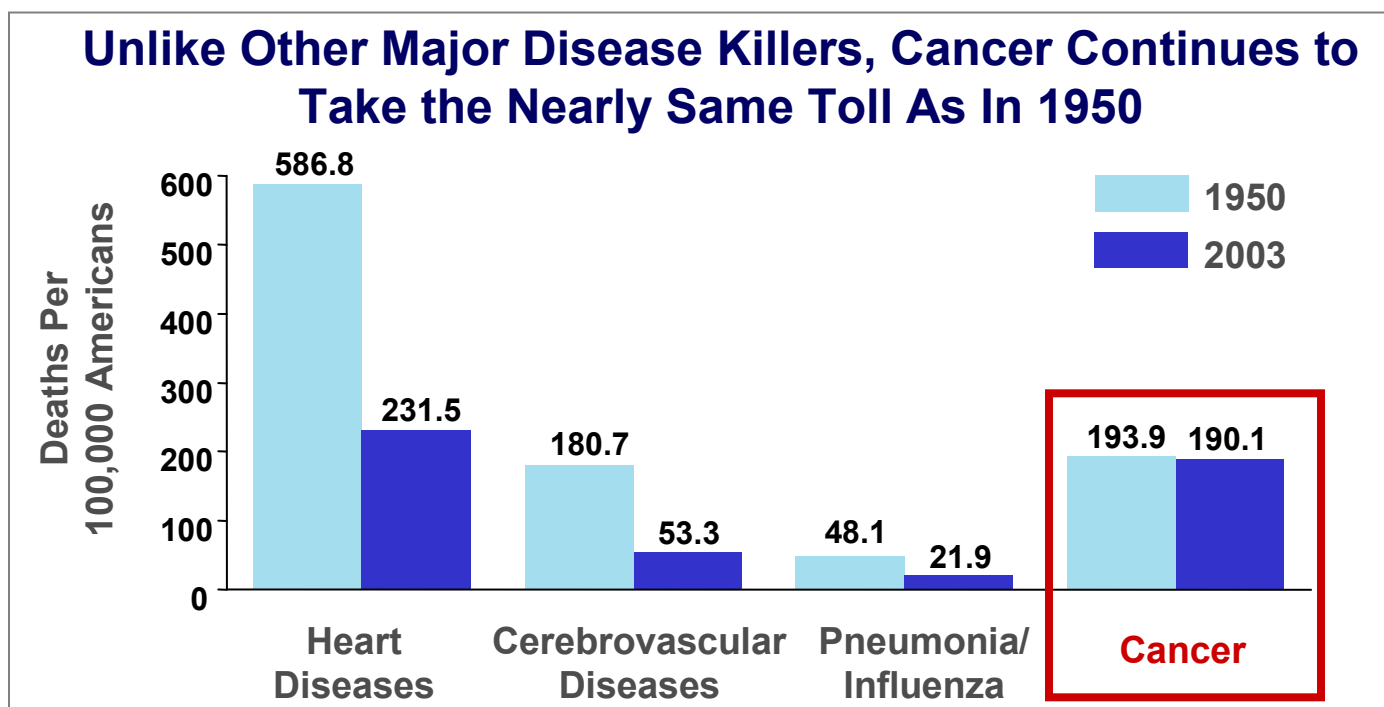
**The Ideal: 21st Century Medicine that is
Predictive, Pre-emptive, Personalized**



Current Cancer Research Environment

Good News: A Drop in Cancer Deaths – Bad News – The Population Impact

- 564,830 Americans died of cancer in 2005
- 1,399,790 Americans will be diagnosed with cancer this year
- \$209.9 billion in 2005 for cancer healthcare costs
- Numbers of new cancer cases will approach 2 million by 2025 (Aging of the baby boomers)

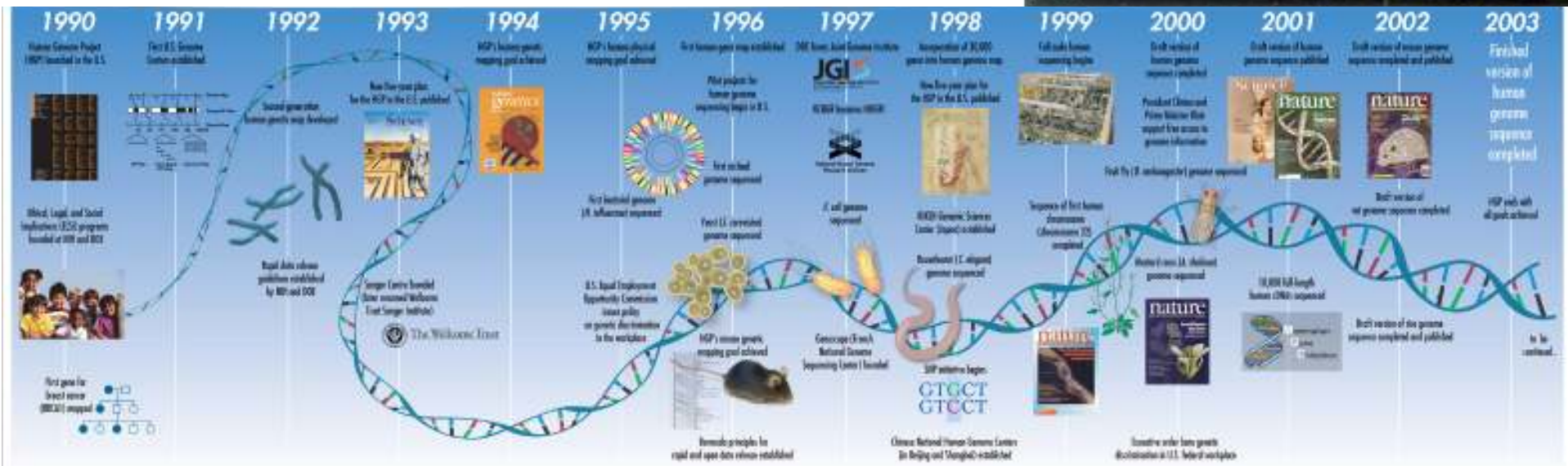
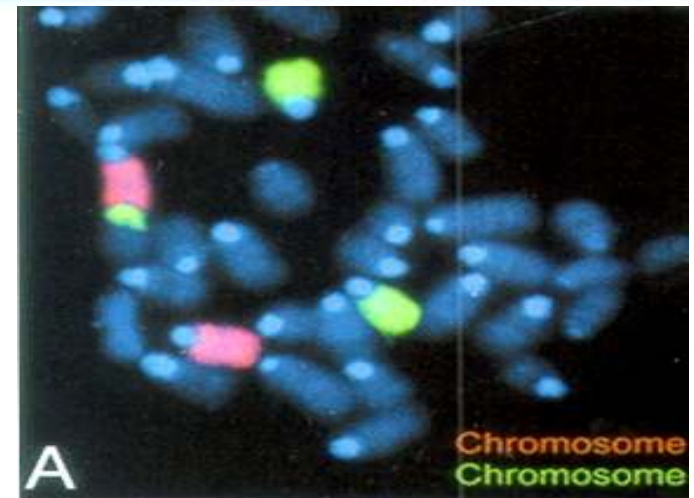


Source for 2006 deaths and diagnoses: American Cancer Society (ACS) 2006 Cancer Facts & Figures; Atlanta, Georgia
Source for 2003 age-adjusted death rate: National Center for Health Statistics, U.S. Department of Health and Human Services, NCHS Public-use file for 2003 deaths.

The Human Genome Sequence – A Landmark Event but Not a Blueprint

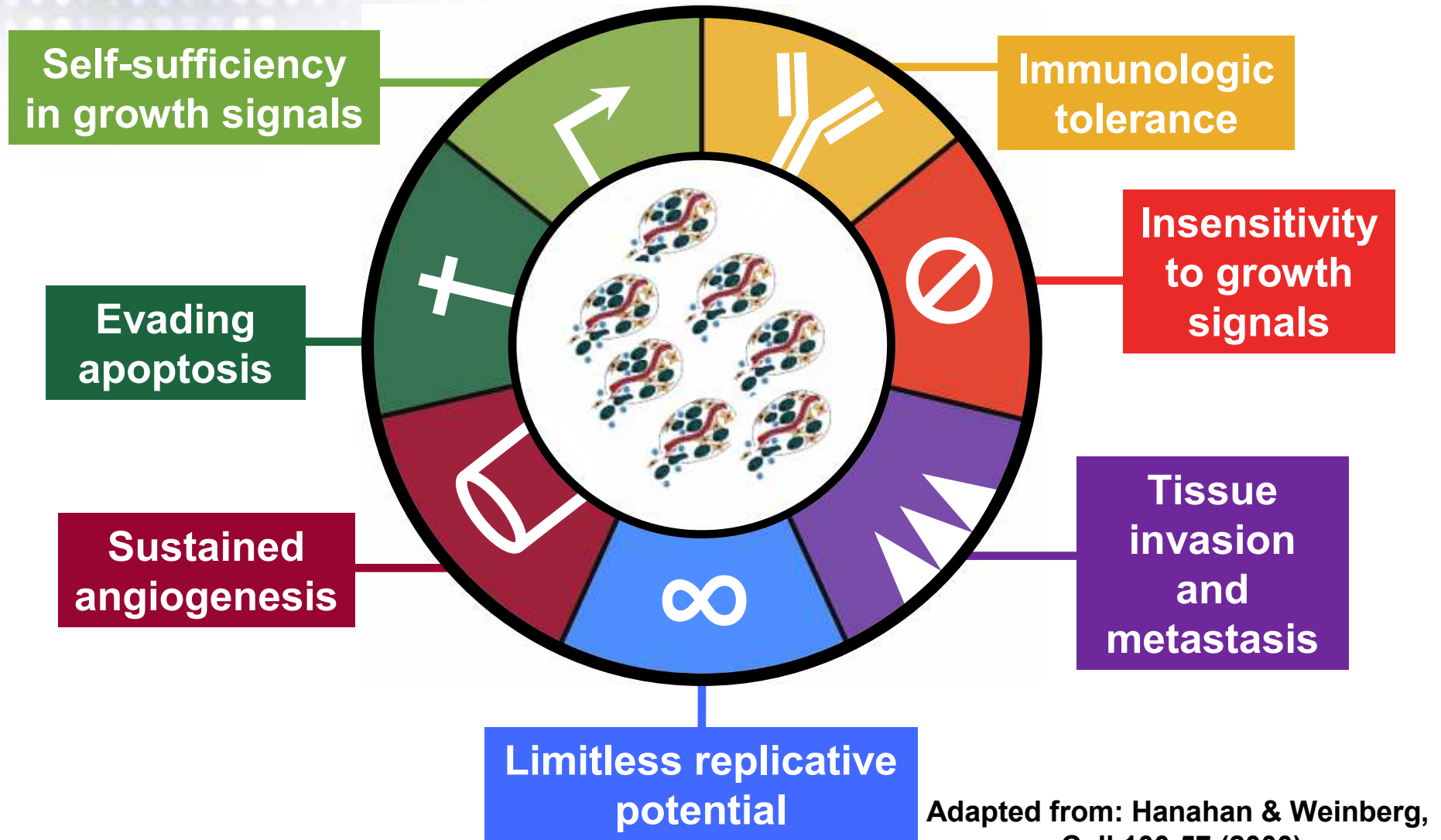
- **Cancer is a “genetic disease”**
(Germline and Somatic Mutations)
- **Types of Genetic Changes:**
Deletions; Amplifications; Mutations;
Translocations; Epigenetic changes*

***Technologies are sophisticated – require high quality biospecimens/biomolecules**



A Landmark Event: The Sequencing of the Human Genome

Understanding the Daunting Complexity of Cancer *(Requires High Quality Biospecimens)*



The Convergence of Molecular Biology, Advanced Technologies, IT and Broadband: Potential for Exponential Progress

Genomics

Proteomics

Metabolomics

Systems Biology

- **Imaging**
- **Chip Technologies**
- **Information Technologies**
- **Nanotechnologies**

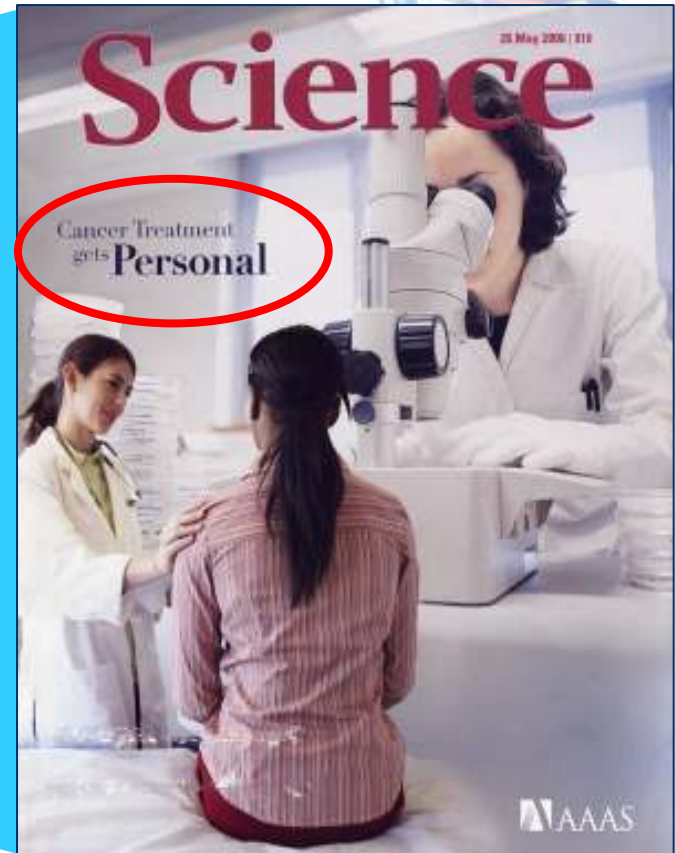
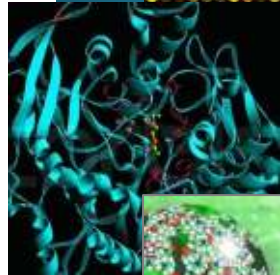
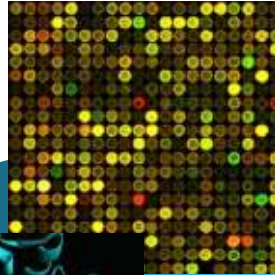


Image courtesy of Science, May 26, 2006

NCI Strategic Investments: An “End to End” System for Development

- **Basic Research and Discovery**
 - ✓ Integrated Cancer Biology
 - ✓ Microenvironment
- **Basic Infrastructure**
 - ✓ **Bioinformatics – caBIG**
 - ✓ Biospecimens – biobanks
 - ✓ Nanotechnology Characterization Lab
 - ✓ Clinical Research (CTWG)
- **Common Technology Platforms**
 - ✓ Biomarkers - Proteomics
 - ✓ The Cancer Genome Atlas Pilot Project
- **Advanced Technologies**
 - ✓ Advanced Imaging
 - ✓ Nanotechnology



Need a New Information Infrastructure for 21st Personalized Century Medicine: NCI 's Approach is The Cancer Bioinformatics Grid (caBIG)

Molecular Data

Clinical Data

Huge and growing volume
of data and multitude of
information systems



caBIG™ is an information network enabling all constituencies in the cancer community – to share data and knowledge to accelerate discovery research, development and delivery of 21st century medicine
to improve patient outcomes



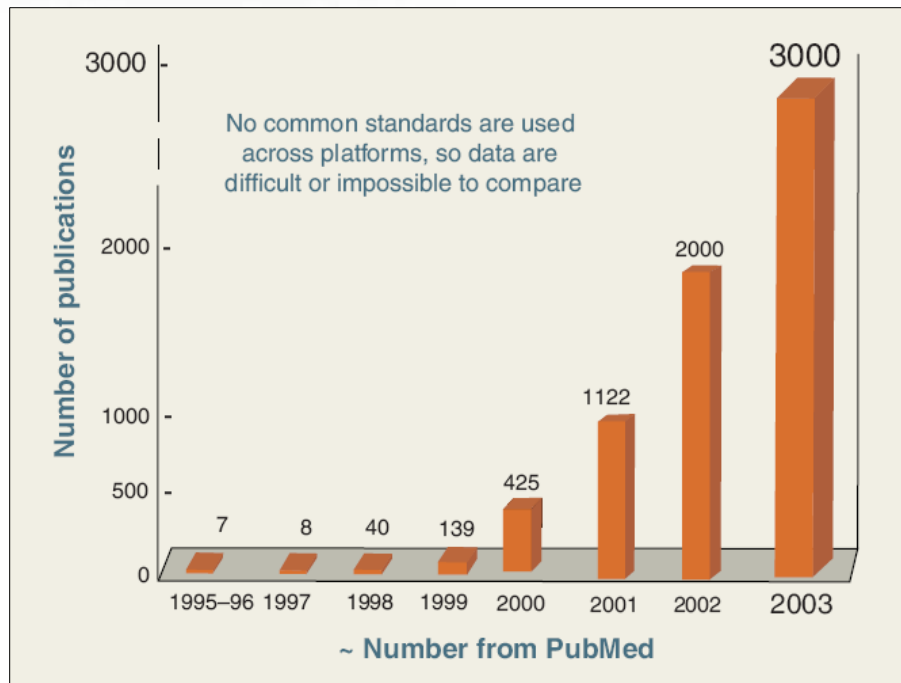
Do We Know that the Quality of Biospecimens Impacts Research Outcomes

Potential Effects of Biospecimen Variables

- Effects on clinical outcomes:
 - Morphological analysis/diagnosis
 - Skewed clinical chemistry results
 - Potential for incorrect therapy when diagnostic is paired with therapeutic (e.g., HER2)
- Effects on research outcomes:
 - Variations in gene expression
 - Variations in post-translational modification (e.g., phosphorylation status)
 - Potential for misinterpretation of artefacts as biomarkers

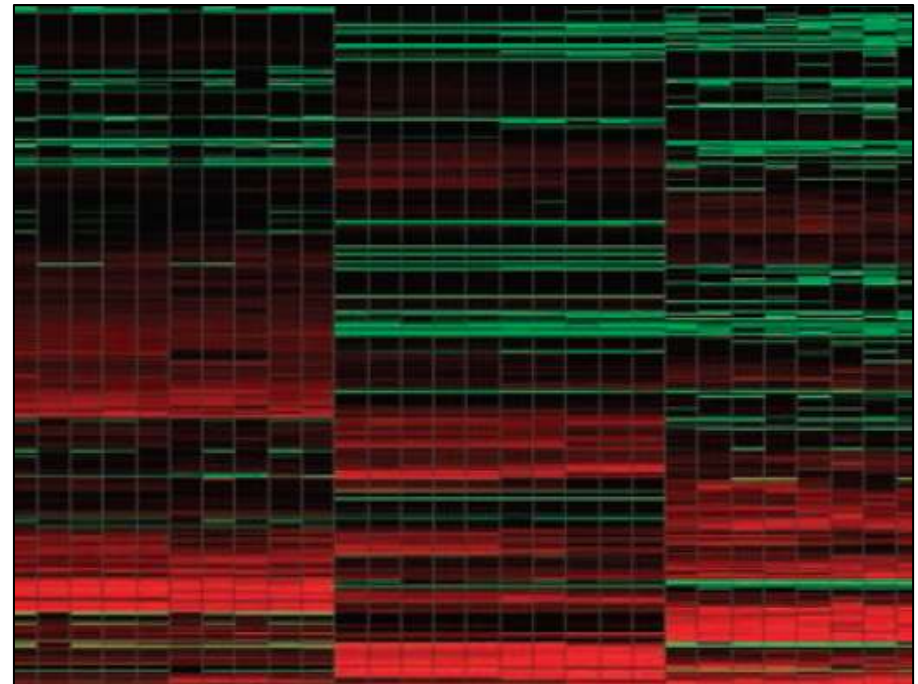
Variable Results in Discovery Research

Rapid Increase in Microarray Publications



Source: SCIENCE, 22 OCT 2004,
“Getting the Noise Out of Gene Arrays”

Results Vary



Map of discordance. An experiment at NIH found that three commercial devices rated different genes as being turned on (red) and turned off (green) in a single batch of pancreatic cells

HER2 Testing

- **HER2 (ERBB2) gene is amplified in ~ 20% of breast cancers**
- **HER2 over-expression (“positive” status): important measure of clinical outcome and recommended therapy**
- **Clinical testing for HER2 status:**
 - **Formalin-fixed paraffin-embedded excised breast tissue:**
 - **Immunohistochemical test (scored 0-3+)**
 - **2+ cases: FISH**
 - **Pathologist uses scoring system to report status**
- **Positive result triggers therapy: \$60K/year**
- **False-positive: risk of cardiotoxicity**



Existing Programs Where We
Know that the Quality of
Biospecimens is Critical

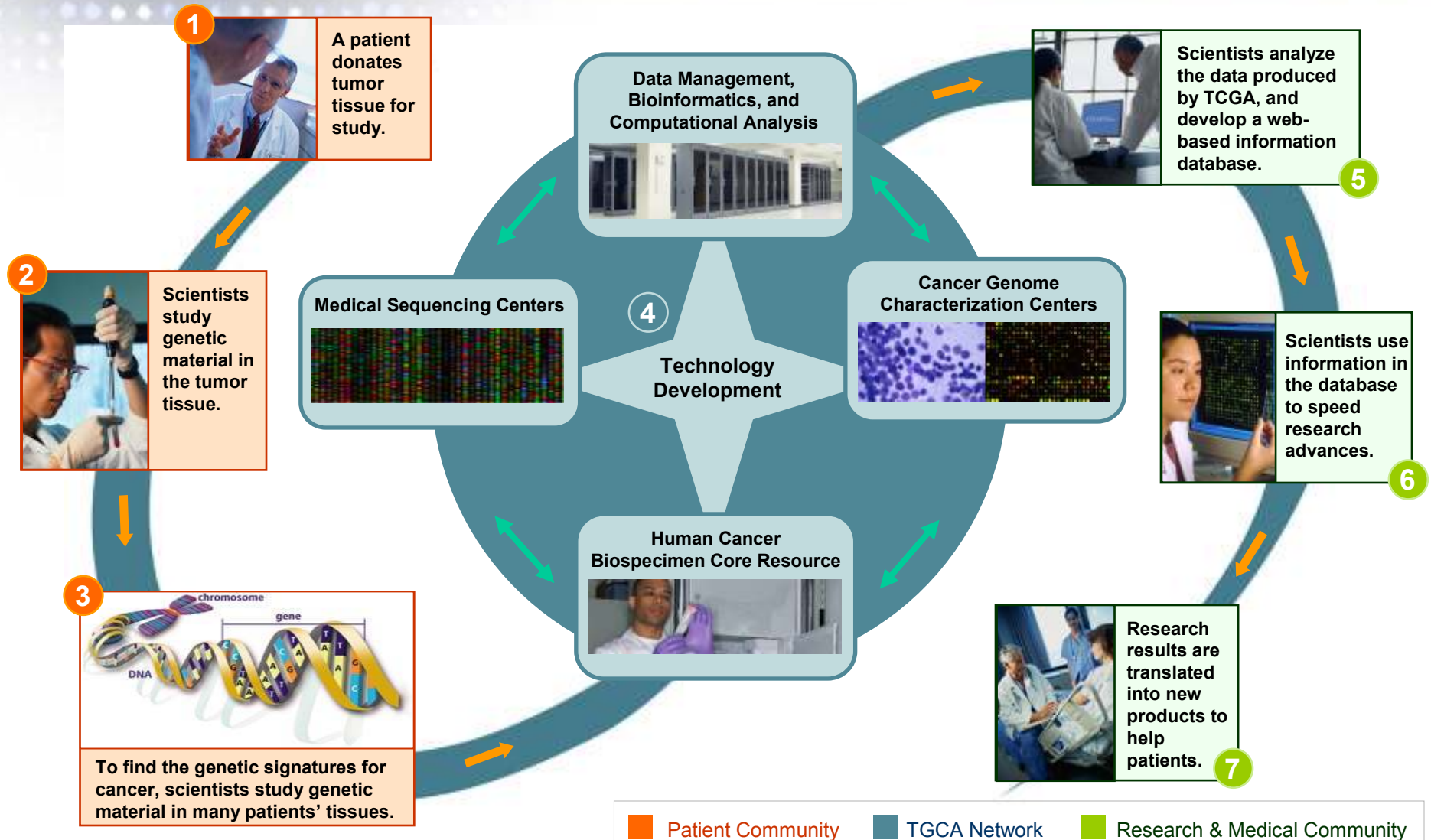
TCGA: A Proactive Collaboration in Medical Genomics

- **The Cancer Genome Atlas (TCGA)** is a three-year pilot project of the **NCI** and the **NHGRI** to increase our comprehensive understanding of the **genetic basis of cancer.**

It is anticipated that TCGA's integrated database of molecular and clinical information will provide unprecedented opportunities to discover and develop a new generation of targeted diagnostics, therapies, and preventives for cancer.

TCGA is large-scale – among other goals, the 3-year pilot is designed to determine the feasibility of undertaking a *full-scale* project to develop a complete “atlas” of all genomic alterations involved in cancer

TCGA: Requires Collaboration and Integration of Several Communities



TCGA Tumor Selection Process

Primary Criteria:

(Must meet all primary qualification criteria)

- At least 250 samples of the same cancer type (combining samples from same cancer type may be pursued to ensure statistical validity)
- Each cancer sample must be accompanied by samples of matched “normal” tissue, such as blood, from the same patient
- Must be from clinical trial or similar study
- A minimum of 0.2 grams of tissue
- Patients gave permission to be re-consented

Secondary Criteria:

▪ *(Collections that met primary criteria were ranked for the following)*

- Quality-control analyses of tissue sample and biomolecules
- Sample characteristics
- Sample collection procedures and storage
- Clinical trial protocol and donor enrollment
- Informed consent
- Clinical data quality
- Clinical data electronic status
- Institution’s contractual capabilities

Telephone Interviews were followed up with site visits by an NCI-NHGRI team

Tumors Selected for Study in the Pilot Project

- **Brain (glioblastoma)**
- **Lung**
- **Ovarian**

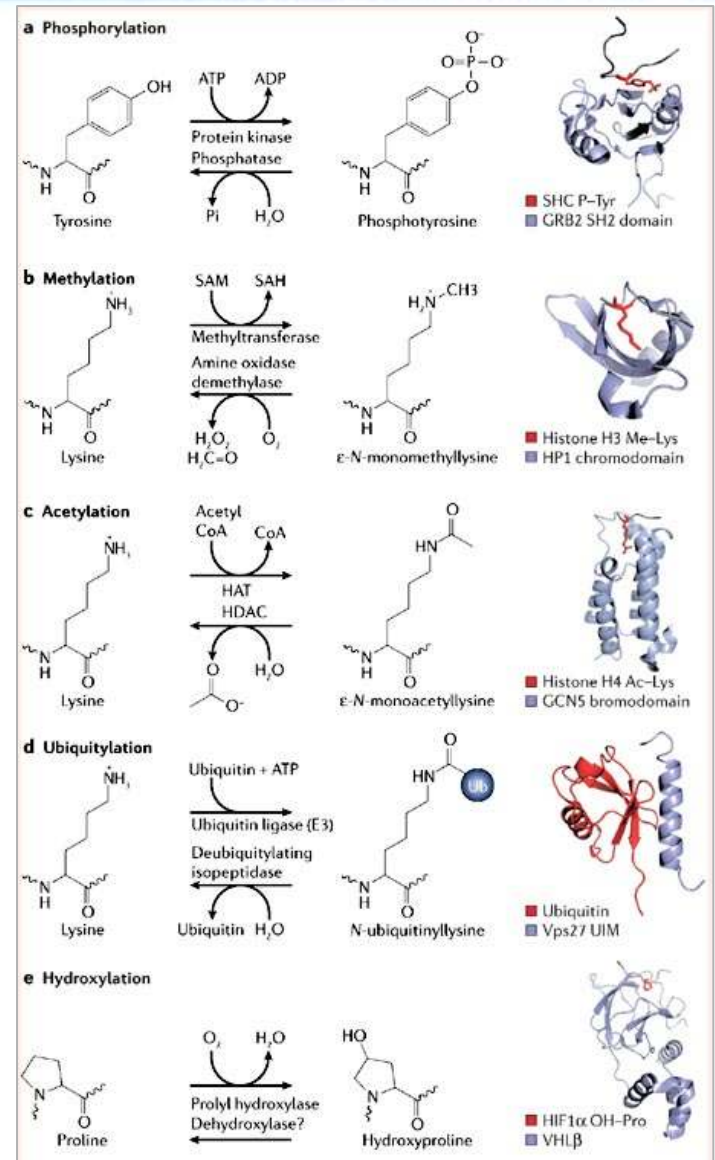
- **These three cancers collectively account for more than 210,000 cancer cases each year in the United States.**
- **They were scientifically interesting, lethal and had biospecimen collections that met TCGA's strict scientific, technical, and ethical requirements.**

Biospecimen Core Resource (BCR): International Genomics Consortium

- **Central to the success of TCGA, the BCR will:**
 - Verify all biologic and clinical data and perform the pathologic QC of qualified tumors from selected existing collections
 - Perform central processing of specimens to provide uniform biomolecules and distribute to both genome characterization and sequencing centers
 - Track and quality assure all specimen-related operations (consent, acquisition, transport, processing, QC, distribution)
 - Provide “standard” samples for technology platform comparisons
 - Develop (with the Office of Biorepositories and Biospecimen Research) and monitor the SOPs for prospective specimen collection
 - Serve as a member of TCGA’s Steering Committee

Proteomics - Exponential Increase in Biological Complexity

- Estimated number of functional human proteins/peptides is anywhere from 100,000 to one million or more
- Complexity is increased by alternative splicing, enzymatic alterations, genome-based variations, differential expression, and posttranslational modifications
- Multiple and integrated technologies will be required to capture this complexity



Seet et al. *Nature Reviews Molecular Cell Biology* 7, 473–483 (July 2006) |

Overcoming Barriers: Clinical Proteomic Technologies Initiative for Cancer (CPTI)

- 5-year, \$104M initiative
- Address early biomarker pipeline issues in proteomic technologies and systems
- Build a foundation of technologies; data; reagents and standards; analysis systems; and infrastructure
- Systematically advance understanding of protein biology in cancer



<http://proteomics.cancer.gov>



NCI's View of the Biospecimen/Biorepository Issues: What We Have Done/Will Do

Definig aBiospecimen Resource *

NCI defines a a biospecimen resource as a collection of human specimens and associated data for research purposes, the physical structure where the collection is stored, and all relevant processes and policies. Biospecimen resources vary considerably, ranging from formal organizations to informal collections of materials in an individual researcher's freezer.

*Source: "First-Generation Guidelines for NCI-supported Biospecimen Resources"

Key requirements for Biospecimen Resources in the Post-Genomic Era

- **Diversity of cancer types and populations represented based on continual review of researcher needs**
- **Access through a timely, centralized peer-review process**
- **Ethical and privacy compliance through a chain of trust**
- **Resources provided without intellectual property restrictions**
- **Pathology and clinical annotation (including longitudinal)**
- **State-of-the-art informatics system to streamline the research production process and create *in silico* research capabilities**
- **Communication and outreach efforts**
- **Best practice and data-driven based SOPs to enable reproducible and comparable (additive) results**

NCI Biospecimen Issues

Heterogeneity in practices among NCI-supported programs has led to a lack of:

- **Common biospecimen resource SOPs, standards, and management principles**
- **Common definitions**
- **Computerized, common access to information on specimens and cases**
- **Common approaches to ethical, legal, and policy issues**

NCI's Biospecimen Activities

2006

- **First-Generation Guidelines for NCI-supported Biorepositories published in Federal Register**

2005

- **NCI Office of Biorepositories and Biospecimen Research established**
- **First International Summit on Harmonization of Biorepositories conducted**
- **caBIG™ software tools for biorepositories developed**

2004

- **Analysis of NCI-supported biospecimen resources conducted**
- **Trans-NCI Biorepository Coordinating Committee formed**

2003

- **Case Studies of Existing Human Tissue Repositories published**
- **National Biospecimen Network (NBN) Blueprint published**

2002

- **Internal and external review process begun**
- **Biospecimen resources identified as critically important to post-genomics cancer research**

NCI Established an Office of Biorepositories and Biospecimen Research

- To establish a chain of trust that begins with the patient and includes institutional review boards, biorepository personnel, and researchers
- To develop best practices based standard operating procedures for:
 - Biospecimen collection, storage, distribution
 - Data collection, including longitudinal data
 - Ethical clearance appropriate for genomic and proteomic studies
- To collaboratively create a state-of-the-art informatics system – building *in silico* capability
- To promoting timely, transparent, peer review-based access of biospecimens and associated data

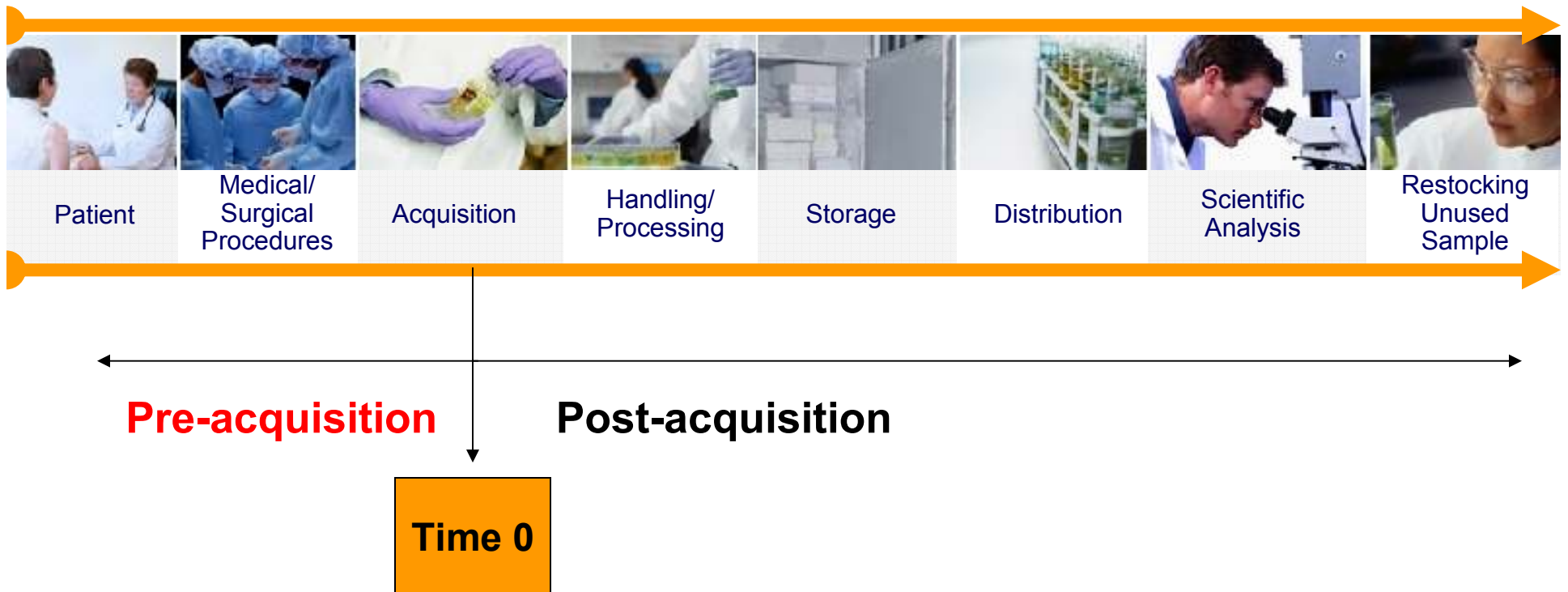
OBBR's Guidelines Development Program

Develop and foster state-of-the-science methods to assess, improve, and assure the quality of NCI's biorepositories:

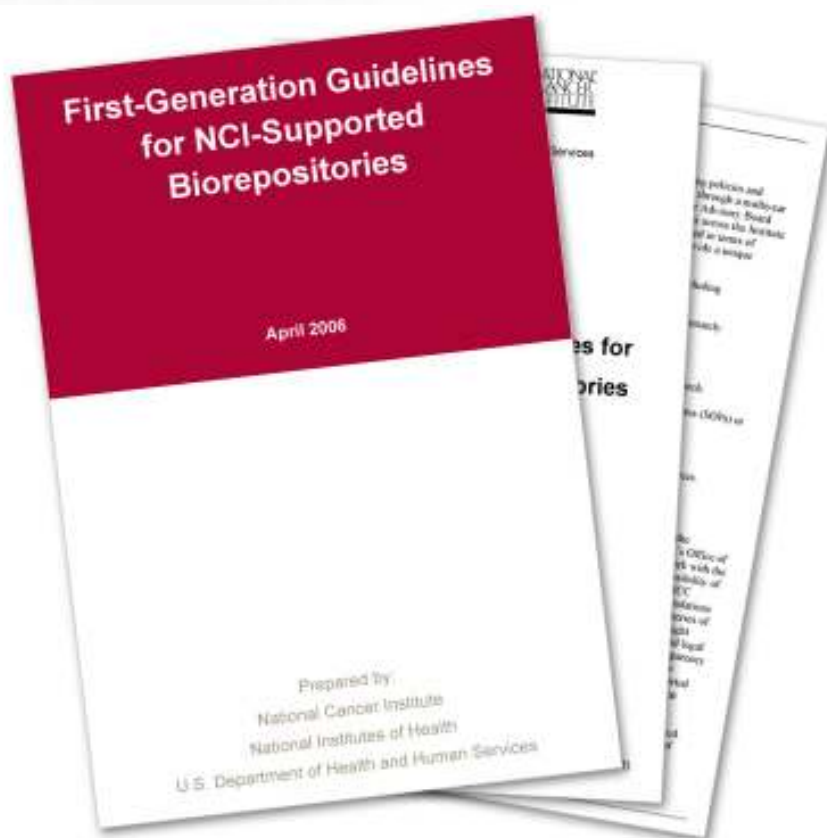
- **First Generation Guidelines for NCI-Supported Biorepositories**
- RAND literature review of biospecimen science publications
- Biospecimen Research Network: generation of new data in biospecimen science
- Collaboration with authoritative professional organizations on data-driven protocol development (e.g., College of American Pathologists)
- Step-wise development of evidence-based Second Generation Guidelines
- Development of objective biorepository evaluation criteria

Lifecycle of a Biospecimen: Biospecimen Research

The specimen is viable



First-Generation Guidelines: Best Practices



Objective:

- **Unify policies and procedures for NCI-supported biospecimen resources***

***previously "biorepositories"**

Guidelines Process

Guidelines were reviewed prior to publication by:

- **NIH Office of Science Policy**
- **DHHS Office for Human Research Protections**
- **NIH Office of Intramural Research**
- **NIH Office of Extramural Research**
- **NIH Office of Technology Transfer**
- **NIH Office of the General Council**

Guidelines were published in the Federal Register:

- **Open public comment period, April-July 3, 2006**
- **Many comments received, on topics including:**
 - **Biospecimen resource economics**
 - **Informed consent requirements**
 - **Definition clarity when designating biospecimen resources affected by the Guidelines**

First-Generation Guidelines Overview

First-Generation Guidelines include recommendations for:

- **Common best practices for research biospecimen resources**
- **Quality assurance and quality control programs**
- **Implementation of enabling informatics systems**
- **Addressing ethical, legal, and policy issues**
- **Establishing reporting mechanisms**
- **Providing administration and management structure (creation of the Office of Biorepositories and Biospecimen Research)**

Informed Consent

- **Use a sample consent template**
- **Consider allowing research participants to specify the types of research for which their specimens may be used**
- **Develop policies for handling specimens for which consent has been withdrawn**
- **Develop clear policies for specimen and data access**
- **Develop policies for obtaining consent for studies involving children**

Access to Biospecimens and Data

- **Develop clear guidelines for sample distribution and clinical data sharing (note: the Guidelines state that protocol-specific requirements should be met before other access is considered)**
- **Ensure that investigators have timely, equitable, and appropriate access, without undue administrative burden**
- **Charge for samples only to recover costs**
- **If a biospecimen resource needs to close, announce the availability of specimens for transfer**
- **Restrict access to subjects' identities and medical, genetic, social, and personal histories via data access system with defined privilege levels**

Privacy Protection/Custodianship

Privacy Protection

- **Protect the privacy of information and follow applicable regulations**
- **Follow documented policies on employee access to data or specimens**
- **Provide levels of security that are appropriate to the type of biospecimen resource**

Custodianship

- **Plans for custodianship of collected specimens and associated data should be part of biospecimen resource protocols**
- **Develop plans to handle/dispose of specimens and associated data:**
 - **At end of the budget period of the grant**
 - **Completion of the specific research objectives of the study**
- **Identify and disclose financial conflicts of interest**
- **Informed consent language should disclose that specimens may help to develop products, tests, or discoveries that may have commercial value**

Intellectual Property

- For the transfer of materials, use a Material Transfer Agreement (MTA) or similar formal agreement
- Biospecimen resource staff are not considered inventors within the meaning of U.S. patent law and have no inherent rights to future intellectual property
- MTAs should specify that research data obtained through the use of biospecimen resource specimens and/or associated data should be made available to the research community

Success Will Depend on Addressing Patient Privacy Concerns (Risks)

- Molecular medicine, including all aspects of genetic-based diagnosis and targeted treatment have heightened patient concerns
 - Ability to collect, track, store, and disseminate clinical and genomic data using new information technology facilitates research, but threaten genetic privacy
- **Protection of patient privacy and confidentiality must be paramount** in developing national resources for molecular medicine
- There are also ethical, ownership, and access concerns

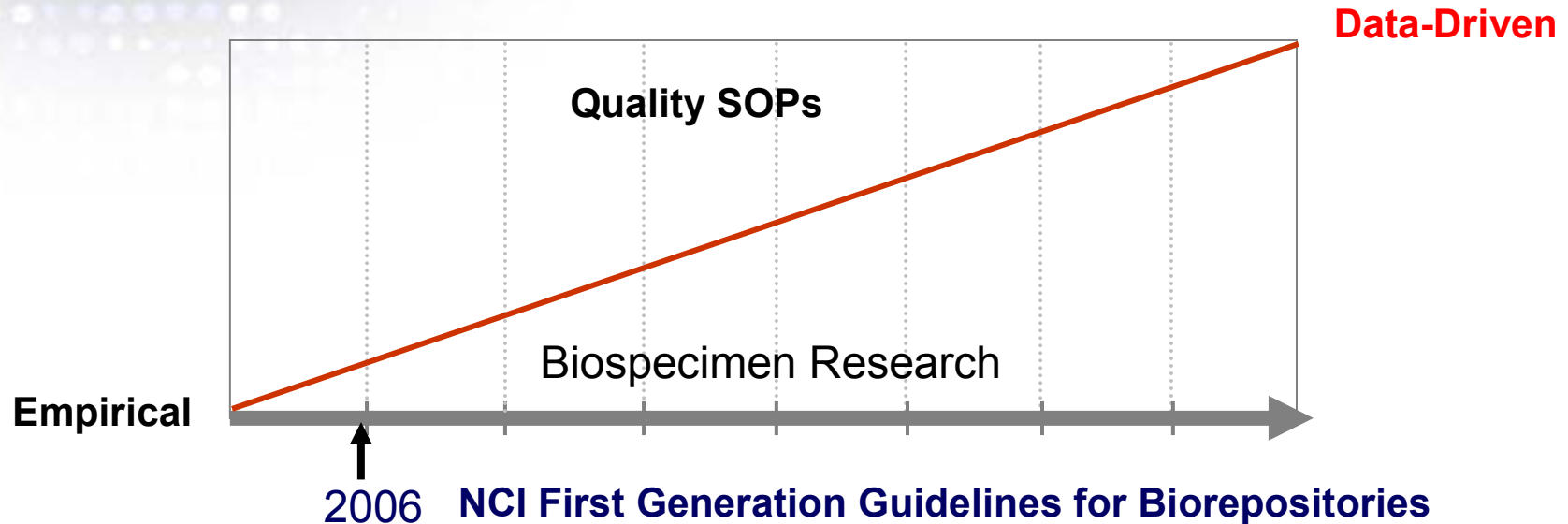
Chain of Trust





The Road Ahead

Personalized Medicine: Requires Scientifically Validated Patient's Biospecimens



Medical/
Surgical
Procedures



Acquisition



Handling/
Processing



Storage



Distribution



QC/QA



Restocking
Unused
Sample

There are a Host of Variables that can Affect the Molecular Integrity of Biospecimens

Biospecimen Variables

Pre-Acquisition

- Antibiotics and other drugs
- Anesthesia
 - Type
 - Duration
- Arterial clamp time
- Blood pressure variations
- Intra-op
 - Blood loss
 - Blood administration
 - Fluid Administration

Post-Acquisition

- Room
 - Temperature
 - Time spent at room temperature
- Fixative
 - Type
 - Time spent in fixative
- Storage
 - Temperature
 - Duration
 - Storage in vacuum

BRN: “Wet” Research

Program Features:

- Interdisciplinary Research with focus on emerging technologies for cancer
- Controlled tissue acquisition
- Controlled molecular isolation and analysis

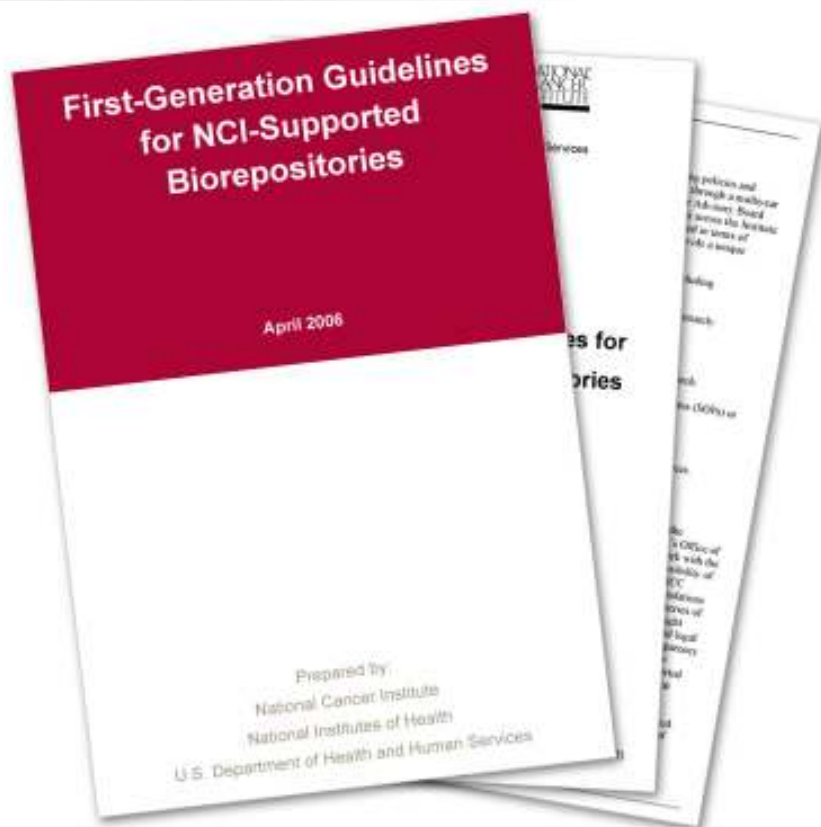
Vision of BRN:

- A network of partners (intramural, extramural, military, professional, and industrial)
- Plan and execute prospective studies
- Determine how the results of DNA, RNA and protein analysis are affected by defined pre-acquisition and post-acquisition specimen variables
- Advisory assistance of scientific experts in tissue acquisition and biomolecule analysis

“Dry” Research: RAND survey

- Comprehensive assessment of the existing published and unpublished information on biospecimen research studies
 - *What important biospecimen research has been done?*
 - *What remains to be done?*
- Currently developing a literature curation tool and database to populate a **publicly available, searchable biospecimen science website**
 - *Central resource for the biobanking community*

Finalize and Implement the First-Generation Guidelines



- **Public comments have been reviewed and revised Guidelines are undergoing clearance at NIH - revision to be posted on Federal Register in late January/early February**
- **Guidelines will be distributed to managers of all NCI-supported intramural and extramural biospecimen resources**
- **Periodic revision will occur with input from researchers, biospecimen resource managers, advocates, policymakers, and related stakeholders as new technologies and clinical practices emerge**
- **Office of Biorepositories and Biospecimen Research will conduct research to establish evidence-based standards for specimen collection, processing, and storage**



OBBR

Office of Biorepositories
and Biospecimen Research

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Role of
Biospecimens

NCI &
Biorepositories

Funding Opportunities and
Demonstration Projects

National
Biospecimen Network

Biospecimen
Sciences

International
Harmonization

Resources

THE CRITICAL ROLE OF BIOSPECIMENS IN CANCER RESEARCH



HIGHLIGHTS:

April 25, 2006
**Guidance on Informed
Consent for *In Vitro*
Diagnostic Device
Studies Using Leftover
Human Specimens that
are Not Individually
Identifiable**

now available for public
comment (view PDF)

Frequently Asked
Questions (more)

Sign Up

Sign up for updates from
hinspecimens.cancer.gov:

First-Generation Guidelines Public Comment Period Now Closed

The Public Comment Period, extended
through July 3, 2006, is now formally closed.

NCI is appreciative of all the comments
received to date, and welcomes ongoing input
from the public.

View guidelines: [PDF](#) [HTML](#)

NCI Leadership Role in Biorepositories

The NCI is leading a national initiative to
systematically address and resolve one of the
most difficult problems that will drive 21st
century cancer research: the limited availability
of carefully collected and controlled, high-quality
human biospecimens annotated with essential

SPOTLIGHT

How Biospecimens are Used in Research

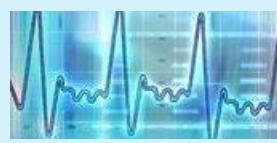
Following the mapping of the
Human Genome in 2001,
biological research has moved
into what is called the "genomic
age". This designation refers to
the ability of scientists to study
disease at the most basic
"molecular" level, by identifying
genes and their function, and
understanding the role genetics
plays in the origin and
progression of disease. ([more](#))

NCI Biospecimen Resources



21st Century Medicine – Will be Information-Driven Based on Partnerships and Multiple Businesses

Patient Information



Current Approach



Resources to Enhance Patient Care



- Differential diagnosis
- Optimization of therapy
- Real-time therapeutic response
- Monitoring for recurrence
- Clinical trial selection
- Information resources for patient

Molecular Based Diagnostics and Treatments – Enabling Prevention

